

Increased Cardiovascular Risk in Breast Cancer Patients

Aumento do Risco Cardiovascular em Pacientes com Câncer de Mama
Aumento del Riesgo Cardiovascular en Pacientes con Cáncer de Mama

RESUMO

Objetivo: O câncer de mama associa-se ao risco cardiovascular aumentado, uma vez que as doenças cardiovasculares são a principal causa de morte não-oncológica nessa parcela populacional. **Método:** O presente estudo do tipo Revisão Integrativa analisou 46 artigos selecionados nas bases PubMed/MEDLINE, SciELO e Europe PMC, objetivando sintetizar evidências sobre os mecanismos fisiopatológicos, agentes cardiotoxicos e estratégias de prevenção e monitoramento cardiovascular em pacientes com câncer de mama. **Resultados:** Os achados evidenciaram que antraciclinas, trastuzumabe, inibidores da aromatase, inibidores de CDK 4/6 e radioterapia torácica são as principais terapias que induzem cardiotoxicidade, e, são potencializadas por fatores de risco como obesidade, hipertensão, síndrome metabólica e menopausa induzida. Biomarcadores cardíacos e strain longitudinal global demonstraram superioridade na detecção precoce de disfunção cardíaca subclínica. **Conclusão:** Portanto, a integração entre cardiologia e oncologia, com estratificação individualizada do risco e acompanhamento longitudinal, são essenciais para redução da morbimortalidade cardiovascular entre pacientes com câncer de mama ou sobreviventes.

DESCRIPTORES: Neoplasias da Mama; Fatores de Risco Cardiovascular; Cardio-Oncologia; Cardiotoxicidade; Saúde da Mulher.

ABSTRACT

Objective: Breast cancer is associated with increased cardiovascular risk, as cardiovascular diseases are the leading cause of non-oncological death in this population. **Method:** This Integrative Review analyzed 46 articles selected from PubMed/MEDLINE, SciELO, and Europe PMC databases, aiming to synthesize evidence on the pathophysiological mechanisms, cardiotoxic agents, and cardiovascular prevention and monitoring strategies in breast cancer patients. **Results:** The findings showed that anthracyclines, trastuzumab, aromatase inhibitors, CDK 4/6 inhibitors, and thoracic radiotherapy are the main therapies inducing cardiotoxicity, and are potentiated by risk factors such as obesity, hypertension, metabolic syndrome, and induced menopause. Cardiac biomarkers and global longitudinal strain demonstrated superiority in the early detection of subclinical cardiac dysfunction. **Conclusion:** Therefore, the integration between cardiology and oncology, with individualized risk stratification and longitudinal follow-up, are essential for reducing cardiovascular morbidity and mortality among breast cancer patients and survivors.

DESCRIPTORS: Breast Neoplasms; Cardiovascular Risk Factors; Cardio-Oncology; Cardiotoxicity; Women's Health.

RESUMEN

Objetivo: El cáncer de mama se asocia a mayor riesgo cardiovascular, siendo las enfermedades cardiovasculares la principal causa de muerte no oncológica en esta población. **Método:** Esta Revisión Integrativa analizó 46 artículos de PubMed/MEDLINE, SciELO y Europe PMC, sintetizando evidencias sobre mecanismos fisiopatológicos, agentes cardiotoxicos y estrategias de prevención cardiovascular en pacientes con cáncer de mama. **Resultados:** Las antraciclinas, trastuzumab, inhibidores de aromatasa, inhibidores de CDK 4/6 y radioterapia torácica son las principales terapias inductoras de cardiotoxicidad, potenciadas por obesidad, hipertensión, síndrome metabólico y menopausia inducida. Los biomarcadores cardíacos y el strain longitudinal global demostraron superioridad en la detección precoz de disfunción cardíaca subclínica. **Conclusión:** La integración entre cardiología y oncología, con estratificación individualizada del riesgo y seguimiento longitudinal, son esenciales para reducir la morbimortalidad cardiovascular en pacientes con cáncer de mama y supervivientes.

DESCRIPTORES: Neoplasias de la Mama; Factores de Riesgo Cardiovascular; Cardio-Oncología; Cardiotoxicidad; Salud de la Mujer.

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INTRODUCTION

Breast cancer is the most common malignant neoplasm among women worldwide, constituting a significant public health problem due to both its prevalence and its associated clinical outcomes. Over the past three decades, cancer mortality has declined significantly as a result of early screening in primary care combined with advanced surgical methods and the most modern therapies available, leading to higher survival rates among patients⁽¹⁾. However, despite the positive impact on the survival of cancer patients, these treatments have led to an increase in morbidity resulting from the adverse effects of modern cancer therapies, such as acute organ damage, particularly in the cardiovascular system⁽¹⁻²⁾. Another factor worth highlighting is the common risk factors shared by

cardiovascular disease (CVD) and breast cancer, which act as predisposing factors for increased cardiac risk in women undergoing antineoplastic therapies, such as: advanced age, smoking, diet, obesity, physical inactivity, and dyslipidemia—which are also factors that influence the development of neoplasms⁽³⁾.

According to the European Society of Cardiology (ESC)⁽¹⁾, current cancer treatments such as chemotherapy, targeted therapies, radiation therapy, and hormone therapy can induce cardiotoxicity; however, this adverse effect is often underdiagnosed due to the current inability to identify and the need to elucidate the long-term effects of these medications, which results in failures to prevent adverse cardiovascular outcomes⁽²⁾. Thus, robust epidemiological studies demonstrate that women with breast cancer have an increased risk of death

from CVD compared to the general population, as found in a systematic review conducted by Gernaat *et al.* (2017), involving more than 1.2 million women with breast cancer, which confirmed a significant increase in the risk of cardiovascular mortality in this population⁽⁴⁾. In another observational cohort study, Bradshaw *et al.* (2017) demonstrated that the risk of death from cardiovascular causes becomes evident on average 7 years after a breast cancer diagnosis in women who received chemotherapy⁽⁵⁾. Similarly, Armenian *et al.* (2016) noted in a retrospective cohort study that cardiovascular diseases among adult female breast cancer survivors represent late effects of cancer therapies, generally occurring after the end of treatment⁽⁶⁾.

Among the main known cardiovascular complications in patients with breast cancer are cardiac dysfunc-

tion—particularly left ventricular dysfunction—and heart failure, in addition to other cardiovascular conditions such as coronary artery disease, arrhythmias, and thromboembolic events⁽⁷⁾.

Among the main chemotherapeutic agents associated with cardiotoxicity in cancer patients are anthracyclines, such as doxorubicin and epirubicin⁽⁸⁾. Anthracycline-induced cardiac dysfunction typically develops approximately 3.5 months after completion of treatment with this class of drugs, with nearly all cases emerging within 1 year of treatment completion⁽⁸⁾. Anthracyclines are responsible for the development of cardiomyopathies characterized by dose-dependent, cumulative, and irreversible cardiac damage, typically manifesting early—such as left ventricular dysfunction—or only decades after the end of chemotherapy treatment⁽¹⁾.

Furthermore, another agent frequently associated with left ventricular dysfunction is an anti-HER2 monoclonal antibody: trastuzumab, which, although it causes functionally reversible cardiotoxicity in most cases, can be clinically significant and dangerous when administered in combination with or sequentially after anthracyclines⁽⁷⁾.

Other non-pharmacological therapeutic modalities, such as thoracic radiation therapy, are also associated with the development of cardiovascular conditions such as coronary artery disease, valvular heart disease, restrictive cardiomyopathy, and constrictive pericarditis⁽⁹⁾. When older techniques for ionizing radiation exposure were used to treat neoplasms, the doses were significantly higher and associated with a greater risk of mortality. Currently, modern techniques have considerably reduced cardiac exposure; however, there remains a significant residual risk that poses a danger to these patients, especially those with preexisting cardiovascular

risk factors⁽¹⁰⁻¹¹⁾.

Consequently, there is a growing need to develop protocols that reinforce the prevention, early assessment, and proper management of cardiovascular complications arising from cancer treatment, with an emphasis on individualized risk stratification before, during, and after breast cancer treatment, in order to promote comprehensive, longitudinal care for these patients⁽¹²⁾. Such actions should prioritize the systematization of strategies that promote integration between the fields of cardiology and oncology, with an emphasis on pre-treatment cardiovascular assessment and continuous monitoring using sensitive biomarkers and imaging studies of the cardiovascular system⁽¹⁾.

Therefore, this article aims to review the available literature on increased cardiovascular risk in patients with breast cancer, discussing the pathophysiological mechanisms involved, the main cardiotoxic agents, modifiable risk factors, and prevention and monitoring strategies, with the goal of providing a basis for clinical management and new strategies that may reduce cases of cardiac dysfunction in patients with breast cancer and post-treatment survivors.

METHOD

This study is an integrative literature review, which allows for a comprehensive synthesis of the scientific knowledge produced on a specific topic based on the analysis of previously published studies with different methodological designs.

The literature search was conducted in electronic databases such as PubMed/MEDLINE, the Scientific Electronic Library Online (SciELO), and Europe PubMed Central (Europe PMC), as these are internationally recognized repositories that provide extensive coverage of the literature in the fields of oncology and cardiology

and make full-text articles available free of charge. The search terms used were indexed in the Health Sciences Descriptors (DeCS), employing the following combined search strategy of keywords and Boolean operators: (“Breast Cancer” AND “Cardiovascular Risk Factors”) OR (“Breast Cancer” AND “Cardiovascular Risk Factor”). The Boolean operators AND and OR were used to broaden the search and sensitivity and select the largest possible number of relevant publications, including studies in Portuguese and English.

Regarding eligibility criteria, studies classified as meta-analyses, systematic reviews, and randomized controlled trials were included, as they represent the highest levels in the hierarchy of scientific evidence regarding cardiovascular risk and cardiotoxicity in patients diagnosed with breast cancer, with the full text available for access in its entirety and published through the year 2026, with no restriction on the initial publication date. Excluded were opinion pieces, editorials, letters to the editor, case reports, and conference abstracts, as well as publications that did not address the association between breast cancer and cardiovascular risk, studies without full-text availability, and duplicate publications identified in more than one database.

The database search strategy resulted in a total of 102 identified publications, with 17 retrieved from PubMed/MEDLINE, 14 from the Europe PMC repository, and 15 from the SciELO platform. The analysis began with a review of the titles, followed by the abstracts; subsequently, the full texts of the preselected articles were read to confirm eligibility, resulting in the final inclusion of 46 articles. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model was used to construct the selection flowchart, in order to visualize each stage of the

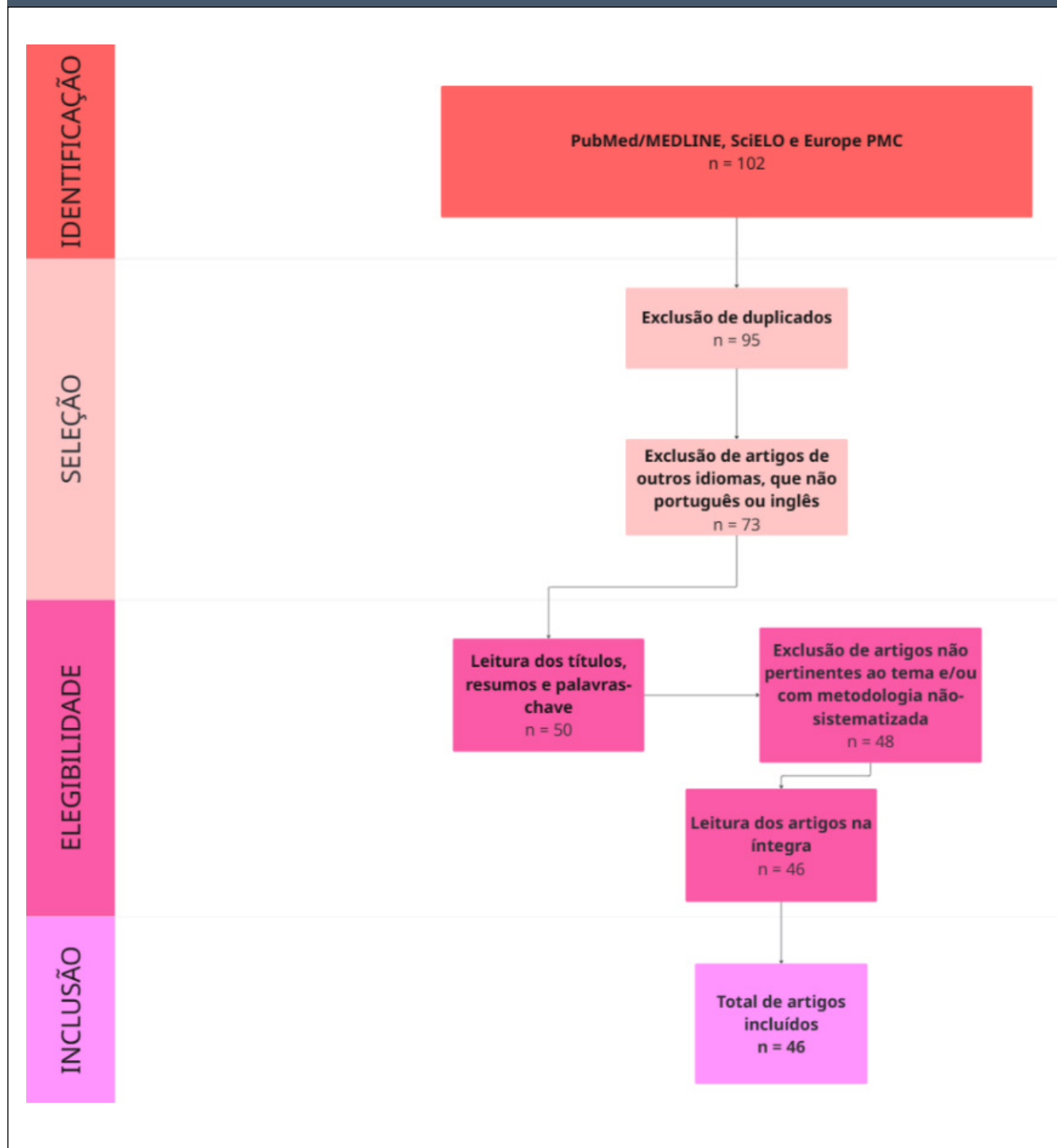
study screening process (Figure 1).

In addition, the studies were subsequently synthesized narratively

and analytically, grouping them by thematic similarity to identify convergences, divergences, and gaps in

knowledge regarding cardiovascular risk in patients undergoing treatment for breast cancer.

Figure 1 - Flowchart for the selection of articles on cardiovascular risk in patients with breast cancer.



Source: Prepared by the authors (2026).

RESULTS

The analyzed articles reinforce that women with breast cancer have a higher risk of morbidity and mortality than the general population⁽¹³⁾. Ng et al. (2024) conducted a meta-analysis that examined approximately 136 studies on breast cancer cases in 16 countries and demonstrated that mortality from cardiovascular disease is significantly higher than in the rest of the population, with variations depending on the type of neoplasm and the diagnosed cardiovascular outcome⁽¹⁴⁾. Among all comorbidities and clinical outcomes, cardiovascular diseases were identified as the leading cause of death not associated with cancer itself⁽¹⁴⁾. Furthermore, another systematic review included data from 14 articles that found that the risk of death from cardiac causes among cancer patients is consistently higher than that observed in the general population, with elevated rates particularly among those undergoing cardiotoxic treatments and with pre-existing cardiovascular risk factors⁽⁴⁾.

Moreover, although therapeutic advances have prolonged the survival of women with breast cancer, this change has led to the current situation where heart disease is the leading cause of death in this population, with an increased and more pronounced risk in the first few years after diagnosis and remaining consistently high in the following years⁽⁵⁾. These findings are consistent with the results reported by Guan et al. (2021), who state that increased breast cancer survival prolongs exposure to the deleterious effects of treatments on cardiovascular health, making continuous monitoring and follow-up of cardiac function a necessity both during active chemotherapy and during remission⁽¹⁵⁾.

In addition to the influence of therapeutic exposure, modifiable and non-modifiable risk factors exert a

significant effect on cardiovascular outcomes and the clinical prognosis of women with breast cancer. Among the modifiable risk factors, a diagnosis of metabolic syndrome was identified as a key determinant in increasing cardiovascular risk; thus, the overlap between the criteria for metabolic syndrome (central obesity, dyslipidemia, hypertension, and hyperglycemia) and the cardiotoxic effects of therapies are factors that synergistically reinforce one another, contributing to increased cardiovascular risk. Thus, studies examining the relationship between these two conditions have found that the prognosis for patients with concurrent diagnoses of cancer and metabolic syndrome is worse from both an oncological and cardiovascular perspective, highlighting the importance of screening and early interventions for both⁽¹⁶⁾. Furthermore, metabolic changes resulting from chemotherapy and hormonal treatments can induce or exacerbate the criteria that characterize metabolic syndrome, contributing to the development of a vicious cycle between cardiovascular risk and cardiotoxicity⁽¹⁶⁻¹⁷⁾.

Other modifiable risk factors should be considered relevant to the cardiovascular risk of cancer patients, particularly with regard to their lifestyle. Thus, a high-risk profile can be characterized by a high prevalence of physical inactivity, poor diet, overweight, obesity, hypertriglyceridemia, and smoking. When combined with cardiotoxicity resulting from anticancer treatments—particularly hormone therapy—this set of factors contributes to an increased risk of adverse cardiovascular outcomes during multidisciplinary follow-up⁽¹⁸⁾. Among these, obesity stands out as an independent risk factor for the development of heart failure in cancer patients, as it modulates the response of cardiac muscle tissue to the action of anthracyclines and trastuzumab;

thus, for every 1 kg/m² in Body Mass Index, there is a 7% increase in this risk⁽¹⁹⁾.

Among the interventions of great importance for reducing cardiovascular risk in this population, associated with modifiable risk factors, are: regular and structured physical activity, dietary changes, weight control, and smoking cessation, since these have a cardioprotective effect by improving left ventricular function and reducing cardiovascular risk markers in women who adopt heart-healthy lifestyle changes before, during, and after cancer treatment⁽²⁰⁻²¹⁾. Similarly, control of systemic hypertension (SH) is an important factor in managing cardiovascular risk, as SH is a pre-treatment predictor of cardiotoxicity that may result from chemotherapy associated with uncontrolled blood pressure levels, particularly in patients with receptor-negative breast cancer⁽²²⁾.

In addition to these factors, it is essential to consider the effects of cancer treatment in menopausal women, since declines in estrogen levels are associated with endothelial dysfunction, atherogenic dyslipidemia, and loss of arterial elasticity—mechanisms that increase the long-term risk of cardiovascular events in postmenopausal women^(11,23).

Among anticancer drugs that induce cardiovascular toxicity, anthracyclines stand out due to their cumulative effects and association with risk factors such as advanced age, hypertension, diabetes mellitus, and obesity, as well as the concomitant use of other cardiotoxic agents, such as trastuzumab⁽²⁴⁾. Among the pathophysiological mechanisms involved in the adverse effects of anthracyclines are: the generation of reactive oxygen species, inhibition of topoisomerase II beta leading to double-strand breaks in the DNA of cardiomyocytes, progressive cellular apoptosis, mitochondrial dysfunction, and fibrosis, which result in the development of irrevers-

ible, dose-dependent dilated cardiomyopathy⁽²⁵⁾. Within this drug class, doxorubicin is identified as a cause of symptomatic heart failure, especially at doses above 400 to 500 mg/m², with a higher likelihood of occurrence in patients with risk factors present prior to treatment⁽²⁵⁾.

Although anthracyclines pose a certain risk to patients undergoing this therapeutic approach, there are strategies that can mitigate these risks, such as selecting other, less cardiotoxic agents from the same class, using a longer infusion regimen, reducing the administered dose, and using liposomal formulations—with clinical benefits in this population widely discussed in the literature^(8,26). Furthermore, these cardiotoxic effects may manifest late, even decades after treatment, which underscores the importance of prolonged and continuous monitoring of ventricular function in female breast cancer survivors, with a peak in these cumulative incidents occurring 1 year after treatment with anthracyclines⁽²⁷⁾.

In addition to hormonal therapies, there are anti-HER2 therapies, such as trastuzumab, a monoclonal antibody targeting HER2 receptors that is widely associated with early treatment-related cardiotoxicity; unlike anthracycline-induced cardiomyopathy, this condition is reversible, not dose-dependent, and managed by discontinuing the medication and providing conventional treatment for heart failure⁽²⁸⁾. The incidence of symptomatic heart failure caused by this agent ranges from 1% to 4%, with approximately 10% of patients presenting a clinically significant left ventricular ejection fraction (LVEF)⁽²⁸⁾. The risk factors most strongly associated with this outcome include prior exposure to anthracyclines, advanced age, a diagnosis of hypertension, and a baseline reduction in LVEF; the sequential or concomitant use of anthracyclines and trastuzum-

ab is characterized as the scenario with the highest cardiovascular risk, in which the rate of cardiac dysfunction can reach up to 27% of cases⁽²⁹⁾. Among monitoring options, regular echocardiography can aid in identifying and preventing the progression of subclinical heart failure to clinical and symptomatic heart failure, with evidence that this diagnostic modality supports the early treatment of reduced LVEF using beta-blockers and angiotensin-converting enzyme inhibitors⁽²⁹⁾.

Aromatase inhibitors (AIs) are used as adjuvant therapy for hormone-receptor-positive breast cancer; however, they may exert a cardiotoxic effect by suppressing serum estrogen levels, which deprives the endothelium and myocardium of the cardioprotective effects of this hormone⁽³⁰⁾. Thus, the use of AIs is associated with an increased risk of high-mortality cardiovascular events, such as stroke and heart failure, primarily due to their deleterious effects on the lipid profile—including increased LDL cholesterol concentrations and reduced HDL levels—as well as the inhibition of the vascular response to the development of atherosclerosis⁽³⁰⁾. In comparison, tamoxifen has protective effects on the lipid profile; however, it poses a higher risk of thromboembolic events than AI⁽³¹⁾. Furthermore, prolonged use of AI for more than 5 years is associated with a higher cumulative incidence of coronary artery disease and ischemic cerebrovascular diseases in female breast cancer survivors⁽³²⁻³³⁾.

For the treatment of locally advanced and/or metastatic hormone receptor-positive, HER2-negative breast cancer, CDK 4/6 (cyclin-dependent kinases 4 and 6) inhibitors—such as palbociclib, ribociclib, and abemaciclib—are often used, representing significant therapeutic advances in cancer treatment. However, recent evidence highlights their

cardiotoxic potential, with important differences in the safety profile among these three agents. Ribociclib is one of the most widely used agents and stands out for reducing the risk of mortality; however, it has been associated with a higher risk of abnormalities in cardiac electrical activity, such as QT interval prolongation, while palbociclib has demonstrated a safer profile but has been associated with an increased risk of thromboembolic events⁽³⁴⁾.

Furthermore, the cardiovascular event most commonly associated with the use of this class of anticancer drugs was hypertension, particularly when CDK 4/6 inhibitors are combined with endocrine therapy, which directly influences the multidisciplinary team's decision regarding electrocardiographic and blood pressure monitoring during their administration^(31,34).

Therapeutic radiation therapy is a treatment modality of great importance for overall survival and progression-free survival, commonly combined with chemotherapy; however, its potential to cause cardiovascular damage is widely discussed in the literature. The pathophysiological mechanisms involved in cardiotoxicity resulting from exposure to radiation therapy stem primarily from its effects on endothelial inflammation, myocardial fibrosis, and the formation of atherosclerotic plaques, leading to the development of cardiovascular conditions such as coronary artery disease, constrictive pericarditis, valvular heart disease, and restrictive cardiomyopathy⁽¹⁰⁾.

Compared to conventional techniques, more modern radiation treatment plans, such as intensity-modulated radiation therapy (IMRT) and deep inspiration breath-holding (DIBH), have yielded significant results in reducing the average cardiac dose, especially for patients undergoing treatment for left-sided breast

cancer⁽³⁵⁾. The risks of cardiac complications, such as coronary atherosclerosis, related to radiation therapy can occur up to 5 years later and persist for about 30 years after completion of oncology treatment⁽¹¹⁾. Thus, transthoracic echocardiographic evaluation is among the strategies for preventing and monitoring myocardial complications, particularly in asymptomatic patients or those at high cardiovascular risk who have undergone thoracic irradiation⁽³⁶⁾.

Given the challenges in preventing complications, current strategies for the early detection of cardiac dysfunction include monitoring cardiac function by measuring the left ventricular ejection fraction⁽³⁷⁾. High-sensitivity troponin T and I and B-type natriuretic peptide (BNP/NT-pro-BNP) are highly relevant markers for predicting cardiovascular events, since even small elevations may indicate ventricular dysfunction over an average period of 12 months, even in the absence of clinical manifestations⁽³⁸⁾. Additionally, global longitudinal strain (GLS)—a measure of cardiac function obtained via speckle-tracking echocardiography—can also aid in the early detection of subclinical cardiac dysfunction, as it provides an early window of opportunity for the use of cardioprotective medication; however, the data are still insufficient to affirm its superiority compared to the conventional measurement of left ventricular ejection fraction (LVEF)⁽³⁷⁾. In contrast, initiating cardioprotective treatment after detecting changes in GLS significantly reduced the decline in LVEF to normal levels⁽³⁷⁾. A relative reduction of more than 15% in GLS indicates that myocardial cells are under stress and have reduced contractile deformability; even in the absence of a significant decline in LVEF, this value should be considered a warning sign of cardiotoxicity⁽³⁷⁾.

Therefore, the importance of strategies such as early multimodal car-

diac evaluation, a multidisciplinary and integrated approach to cancer treatment, and cardiovascular risk management in women with breast cancer must be emphasized, particularly with regard to early detection, timely and evidence-based intervention, and strengthening communication between the fields of cardiology and oncology during the follow-up of these patients⁽³⁹⁾. Among the strategies that can be implemented by cardiology and oncology professionals are pre-treatment cardiac evaluation, individualized risk stratification, and cardiovascular monitoring during cancer treatment—even when resources and access to specialists are limited—in order to establish a care framework focused on preventing adverse cardiovascular events⁽⁴⁰⁻⁴¹⁾.

DISCUSSION

The articles reviewed in this integrative review demonstrate that the increased cardiovascular risk in women with breast cancer is a multifactorial phenomenon, relevant to patient prognosis and recognized as one of the leading causes of morbidity and mortality in this population. Furthermore, it has been consistently stated that the mechanisms of action of oncological therapeutic methods and their interactions, preexisting cardiovascular risk factors, and metabolic changes resulting from neoplasms constitute a complex foundation for reduced survival in these patients, contributing to increased cardiac risk throughout follow-up and even decades after treatment ends.

Therefore, to understand the effects of cancer therapy on the development of cardiotoxicity, it is important to highlight the pathophysiological mechanisms involved in this outcome. Among the main mechanisms of cardiac toxicity are: the generation of reactive oxygen species, mitochondrial dysfunction, activation of pro-inflammatory pathways and

the release of cytokines and growth factors, and cellular apoptosis with gradual and irreversible loss of cardiomyocytes, culminating in fibrosis and remodeling of the cardiac chambers, as well as vasoconstriction and thrombosis, which lead to hypoperfusion, microvascular thrombosis, and ischemia-induced cell death^(35,42). Associated with this, damage to endothelial cells promotes systemic vascular dysfunction, which manifests as increased vascular permeability, acceleration of the atherosclerotic process, and an increased risk of cardiac ischemia. Such changes can lead to progression of the condition to dilated or restrictive cardiomyopathy, arrhythmias, and sudden cardiac death, as well as electrocardiographic abnormalities such as QT interval prolongation and bradyarrhythmias⁽⁴³⁾.

Furthermore, it is important to differentiate between the types of cardiotoxicity and the influence of antineoplastic drugs on their development. Type I cardiotoxicity is irreversible, dose-dependent, and cumulative, whereas type II cardiotoxicity is reversible and not dose-dependent; this distinction must be made clinically to enable safer and more accurate decision-making by the oncology team safer and more accurate—both in guiding the selection of the most appropriate treatment regimens and in interventions involving modifying, discontinuing, or restarting treatment with a specific drug in the face of clinical signs of cardiovascular compromise^(8,26).

Thus, studies have revealed the clinical implications of each therapeutic class used against breast cancer and their different mechanisms of cardiotoxicity. Anthracyclines act by inhibiting topoisomerase II beta in cardiomyocytes, inducing double-strand DNA breaks and leading to progressive cellular apoptosis; thus, their deleterious effects result in a pattern of irreversible, cumulative,

dose-dependent, and delayed-onset cardiotoxicity⁽²⁷⁾. These findings have broadened the perspective regarding the development of strategies for cardioprotection while preserving the efficacy of antitumor treatment, such as the use of dexrazoxane and liposomal anthracycline formulations with reduced penetration into the myocardium⁽²⁷⁾.

Furthermore, aromatase inhibitors have also shown evidence of cardiovascular effects and the underlying cardiotoxic mechanism. These agents induce estrogen deprivation in women, since they are used to treat cancers with estrogen receptors (HER2 receptors); thus, there are deleterious effects on lipid metabolism, endothelial function, and arterial stiffness⁽³⁰⁾. Therefore, these agents differ from the direct cardiotoxic mechanism of anthracyclines and trastuzumab, since the outcomes resulting from their administration develop secondarily and are clinically associated primarily with postmenopausal women who have pre-existing cardiovascular risk factors and have been using hormone therapy for more than 5 years⁽³⁰⁾.

Exposure of cardiac tissues to thoracic radiation therapy, even at moderate doses of ionizing radiation, triggers a cascade of damage that results in endothelial inflammation, myocardial fibrosis, accelerated atherosclerosis, and valvular dysfunction, primarily in the pericardial tissue, coronary arteries, and left ventricle⁽¹⁰⁾. Furthermore, these effects manifest late, which poses a challenge for the early detection of such cardiovascular events; additionally, factors such as the overlap of cardiac symptoms with other health issues and the fact that cancer treatment and clinical follow-up are conducted in different departments also hinder their recognition⁽¹⁰⁾. Currently, modern techniques such as deep-inspiration brachytherapy (DIBH) and intensity-modulated radiation therapy

(IMRT) offer a safer profile for cancer treatment; however, the residual risk remains clinically significant, especially in women with multiple cardiovascular risk factors, for whom even low doses of radiation to the myocardial tissue can lead to complications and adverse outcomes⁽³⁵⁾. Studies emphasize the importance of long-term cardiovascular surveillance through the implementation of structured protocols, including periodic examinations such as echocardiography, exercise testing, and evaluation for cardiac ischemia, particularly among female breast cancer survivors who have previously undergone radiation therapy—especially those treated in the left hemithoracic region, where the heart is more exposed⁽³⁶⁾.

It is worth noting the importance of comparing scientific knowledge with clinical practice, since—even with evidence highlighting the prevention and management of anthracycline-induced cardiotoxicity through the use of analog agents that are less harmful to the heart and through liposomal formulations—long-term cardiac function monitoring remains the most effective strategy for preserving cardiac function in everyday clinical practice⁽⁴⁴⁾. This finding demonstrates the growing need for specialists in the field of cardio-oncology to be able to detect the mechanisms of cardiotoxicity associated with antineoplastic drugs, since increasing therapeutic advances are directly linked to a broader spectrum of cardiovascular complications requiring monitoring in women undergoing treatment for breast cancer⁽⁴⁵⁾. The proposed multidisciplinary approach is based on the early detection of cardiac impairment through biomarkers and imaging tests, prevention through the monitoring of modifiable risk factors before, during, and after treatment, and the management of symptomatic cardiac dysfunction with beta-blockers, angiotensin-con-

verting enzyme inhibitors, and angiotensin receptor blockers, with the goal of ensuring the feasibility of cancer treatment with minimal impairment to cardiac function⁽⁷⁾.

Furthermore, continuous monitoring should also extend to the post-treatment period, since cardiovascular risk is not limited solely to the period of exposure to anticancer agents but also persists over the subsequent years. Of particular note are the components of metabolic syndrome—a common risk factor among female breast cancer survivors—which create an adverse cardiometabolic environment that synergistically interacts with the damage induced by the use of anthracyclines, trastuzumab, and radiation therapy, resulting in a progressive and cumulative cardiovascular risk that can persist for years after treatment ends⁽¹⁶⁾. In addition to metabolic syndrome, early menopause induced by certain anticancer agents, such as aromatase inhibitors, is also an additional risk factor due to the metabolic changes caused by this state of hypoestrogenism⁽¹⁷⁾.

Therefore, it is emphasized that the most effective and promising strategy for reducing morbidity and mortality in this population segment must be based on patient-centered and individually tailored care models, with follow-up planning based on the type of therapeutic exposure and each woman's previous and current cardiovascular conditions. Furthermore, continuous monitoring and follow-up methods should be combined with structured intervention programs that incorporate lifestyle modification strategies, screening for metabolic syndrome, serial cardiovascular assessment, and the maintenance of effective communication among the different sectors and services involved in these women's healthcare, whether in primary care or specialized settings⁽⁴⁶⁾.

Among the limitations of this

study, the differing methodologies across the collected articles stand out—ranging from randomized clinical trials and systematic reviews to observational cohort studies—which may influence comparisons of results and limit the drawing of conclusions regarding the magnitude of the current epidemiological landscape of cardiovascular complications in women with breast cancer. Furthermore, the definition of cardiotoxicity across the articles proved to be heterogeneous and variable, with differences also observed in the assessment methods used to measure cardiac function and in the follow-up periods suggested by the authors.

Therefore, future studies should prioritize the development of accurate predictive models for cardiovascular risk analysis in patients with breast cancer, as well as address the impact of cardioprotective interventions in patients at high cardiac risk, in addition to conducting longitudinal studies spanning more than 20 years of periodic evaluation of female breast cancer survivors.

CONCLUSION

This integrative literature review

confirmed, based on scientific evidence of high methodological quality, that the increased cardiovascular risk in patients with breast cancer constitutes a significant, multidimensional clinical and h y problem of growing relevance in the context of cancer care.

The data collected demonstrated that cardiovascular diseases are the leading causes of death unrelated to breast cancer in women previously diagnosed with the disease; thus, these conditions should not be investigated and treated independently, since they share common risk factors, interact with one another, and reinforce each other, in addition to being epidemiologically relevant as causes of morbidity and mortality in a population segment that has been showing progressively longer survival.

The synthesized evidence also confirms the need to implement structured cardio-oncology care protocols, integrating pre-treatment cardiovascular assessment, periodic monitoring using biomarkers and imaging methods during treatment, and post-treatment cardiovascular health follow-up. Therefore, to ensure minimal long-term cardiovascular effects and improve the quality of life for

female survivors, cardiovascular risk stratification, early identification using cardiac biomarkers, and timely cardioprotective management are urgently needed as strategies during breast cancer treatment. In addition, this underscores the importance of adopting comprehensive, longitudinal, and patient-centered care models that integrate the perspectives of cardiology and oncology, with a focus on multidisciplinary collaboration among the patient support team.

Therefore, the results of this study demonstrate that cardiovascular risk in patients with breast cancer is significant, measurable, clinically relevant, and modifiable through early interventions and individualized treatment. The evidence shows that a fragmented and isolated approach is ineffective and poses a risk of leading women with breast cancer toward worse outcomes and an unfavorable prognosis. For this reason, the establishment of the specialty of cardio-oncology—with well-established protocols and a trained, multidisciplinary, and “ ” team—is essential for the integrated management of these patients and their varying risk profiles.

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